Pharmacotherapy of Asthma

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Overview

- Goals of Asthma Therapy
- Categories of Medications
- Asthma Guidelines and Therapy
- Medications
  - Corticosteroids
  - Beta-agonists
  - Combination medications
  - Leukotriene modifiers
  - Others

Goals of Asthma Therapy

- Prevent and control troublesome symptoms
- Reverse airflow obstruction and maintain normal pulmonary function
- Maintain **normal activity levels**
- Reduce the frequency and severity of exacerbations and ER visits
- Minimize medication adverse effects
- Meet **patients' expectations** of asthma care

Categories of Medications

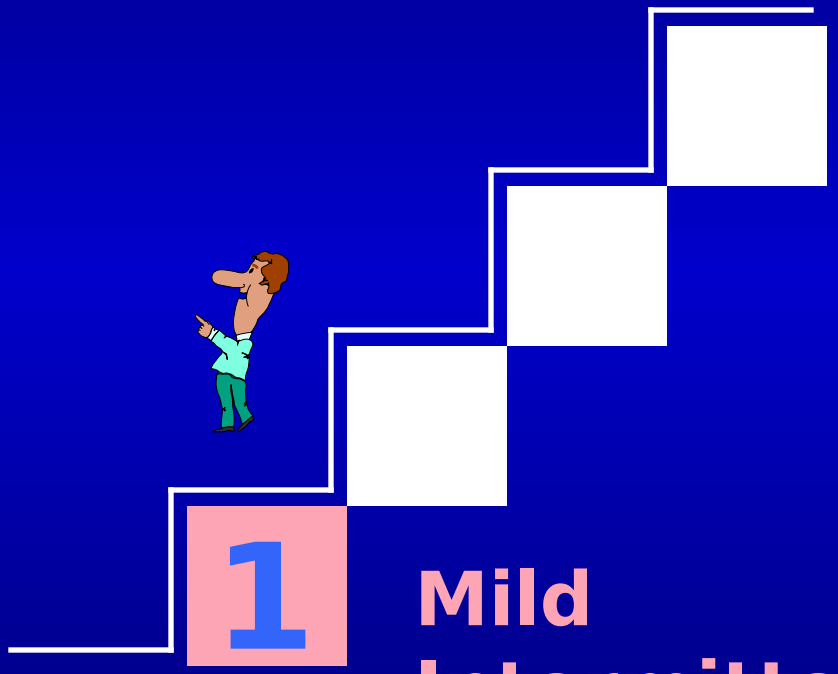
- **Long-term control (maintenance) medications**
  - Corticosteroids
  - Long-acting beta-agonists
  - Leukotriene modifiers
  - Cromolyn and nedocromil
  - Methylxanthines

Categories of Medication

- **Quick relief (rescue) medications**
  - Short acting β-2 agonists
  - Anticholinergics

NAEPP Guidelines Classification of Asthma Severity

NAEPP Guidelines Classification of Asthma Severity



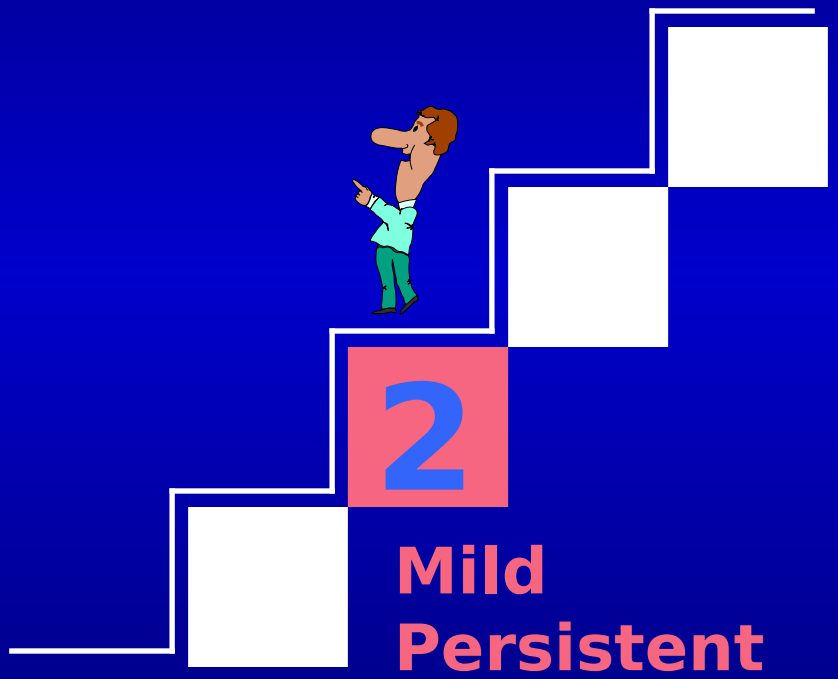
Clinical features before treatment

- Symptoms ≤ 2 x per week
- Brief exacerbations
- Nighttime symptoms ≤ 2 x pe
  month
- Asymptomatic with normal lu
  function between exacerbatio
- FEV_1 and PEF ≥ 80% predict
- PEF variability < 20%

Mild Intermittent - Therapy

- Short-acting inhaled beta-agonists as needed and prior to triggers
  - Albuterol
- A very clear and defined *asthma action plan*
- No long term controller medication

NAEPP Guidelines Classification of Asthma Severity



Clinical features before treatment

- Symptoms > 2 x per week but <1 x per day
- Exacerbations may affect activity
- Nighttime asthma symptoms > 2 x per month

Mild Persistent - Therapy

- Quick Relief
  - Inhaled short-acting beta-agonist PRN
- Long-Term Control
  - **Low dose inhaled corticosteroid (ICS)**
  - May also consider leukotriene modifier, cromolyn, nedocromil
  - For patients with ASA sensitive asthma, consider using leukotriene modifiers

NAEPP Guidelines Classification of Asthma Severity

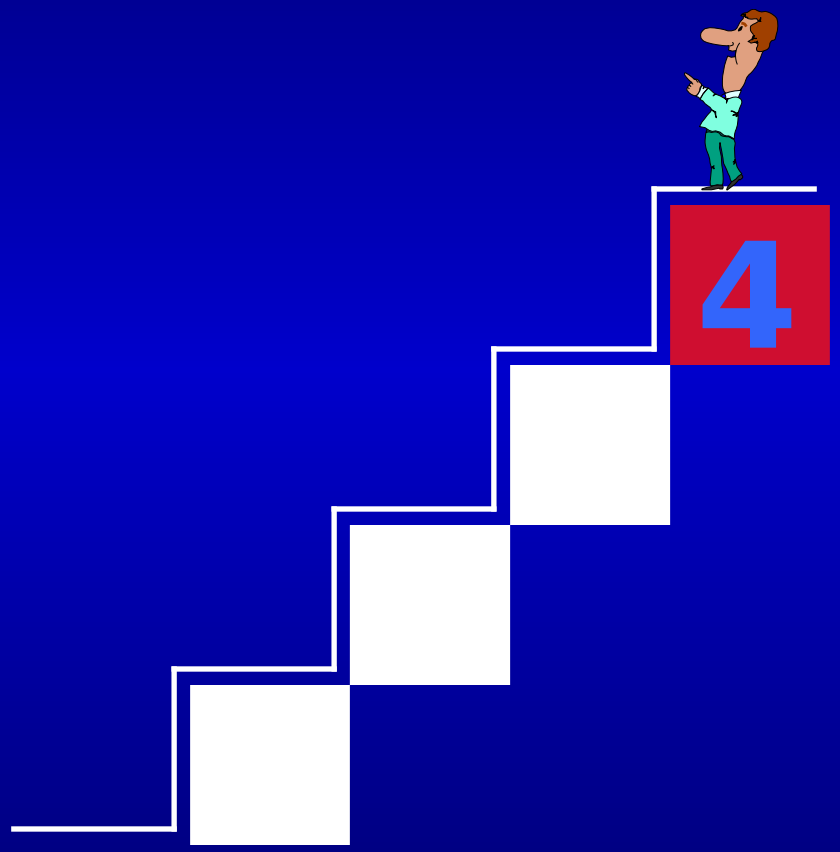
Clinical features before treatment

- Daily symptoms
- Exacerbations ≥ 2 x per week that affect activity
- Nighttime asthma symptoms > 1 x per week
- Daily use of short-acting ß agonist

Moderate Persistent - Treatment

- Quick Relief
  - Short acting inhaled beta-agonist
- Long Term Control
  - **ICS (low-medium dose) with long-acting inhaled beta-agonist OR**
  - **Increase inhaled steroids in medium range**
  - Alternative: Low dose ICS with leukotriene modifier or theophylline
  - If needed: medium-dose ICS with long-acting beta agonist (preferred), leukotriene modifier or theophylline

NAEPP Guidelines Classification of Asthma Severity



Clinical features before treatme

Severe Persistent

- Continuous symptoms
- Frequent exacerbations
- Frequent nighttime sympt
- Limited activity
- FEV_1 and PEF $\leq$ 60% pred
- PEF variability > 30%

Severe Persistent - Therapy

- **High dose ICS with long-acting inhaled beta-agonist**
- If needed, oral steroids
- Usually require multiple controller medications and regular bronchodilator use

Asthma Medications

steroids

Azmacort®
(triamcinolone acetonide) Oral Inhaler
Rhône-Poulenc Rorer
Beclovent®
(beclomethasone dipropionate, USP) Inhalation Aerosol
Glaxo Wellcome Inc.
Vanceril®
(beclomethasone dipropionate, USP) Inhaler
Schering Corporation
Flovent®
(fluticasone propionate) Inhalation Aerosol
Glaxo Wellcome Inc.

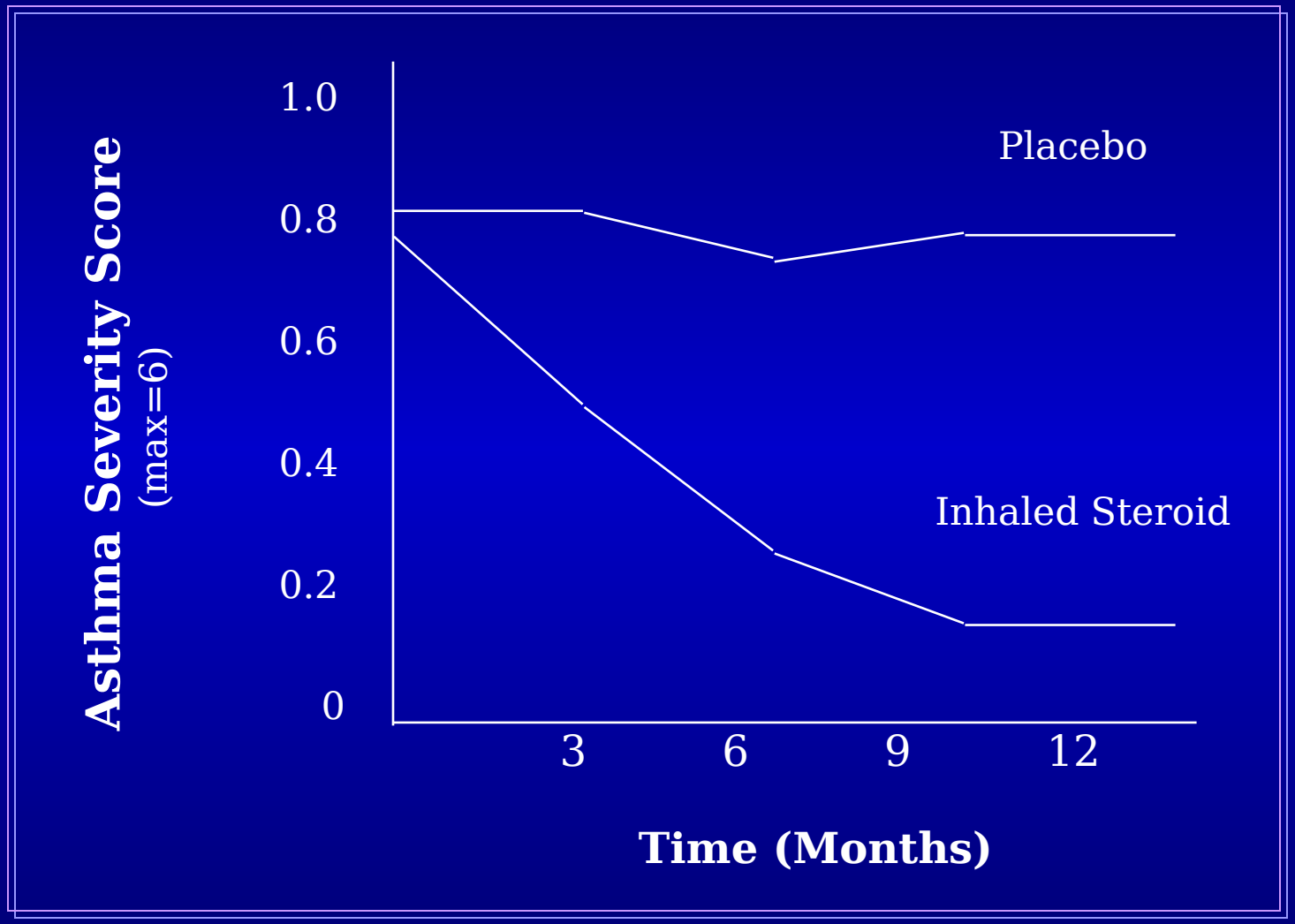
People often think of something like this

Or this

Clinical Effects

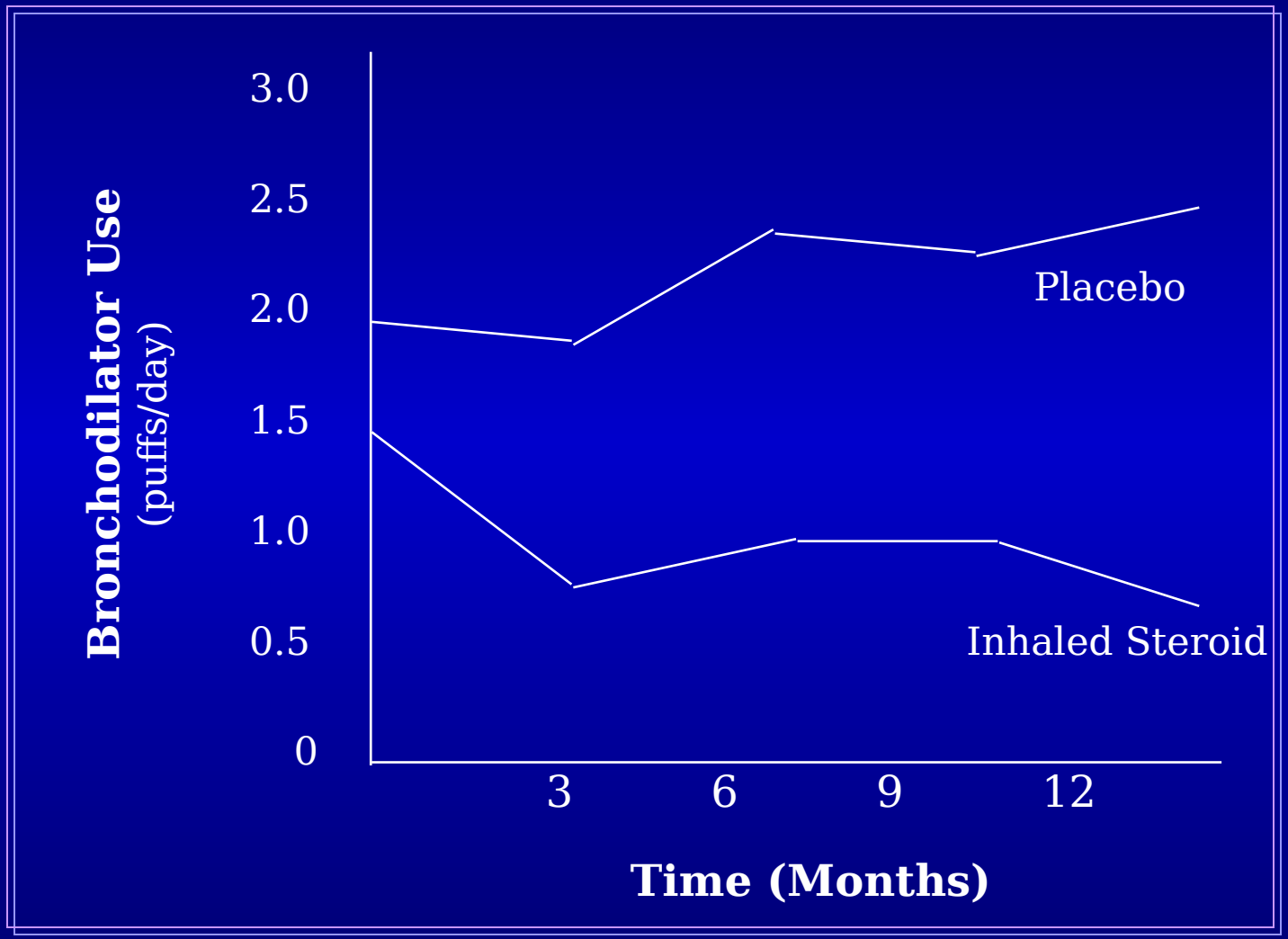
- Corticosteroids are the **most effective treatment** for long term control of asthma
  - Reduce symptoms
  - Decrease use of bronchodilators
  - Improve peak flows
  - Decrease exacerbations
- Let’s look at some examples of existing data

Clinical Effectiveness



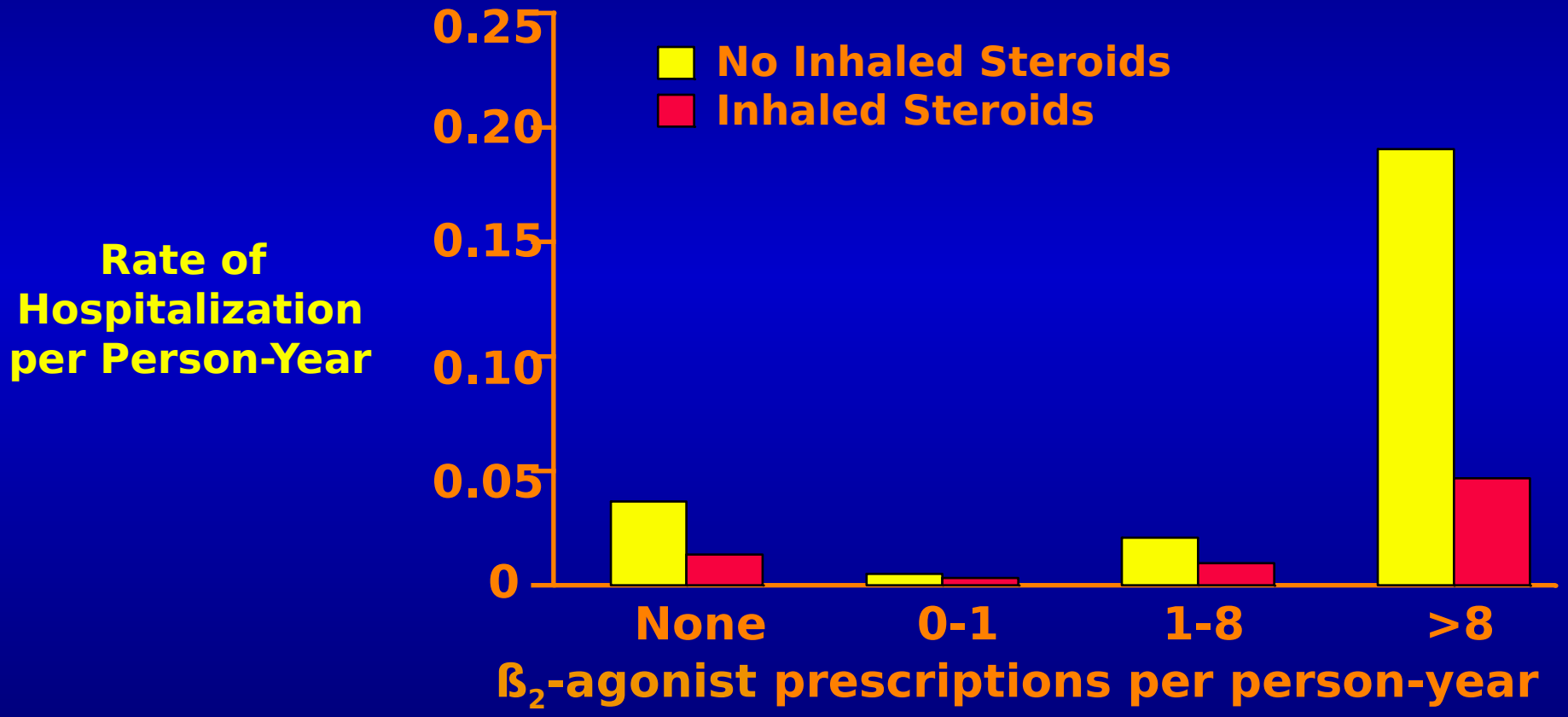
Juniper et al., Am Rev Resp Dis, 1990

Clinical Effectiveness



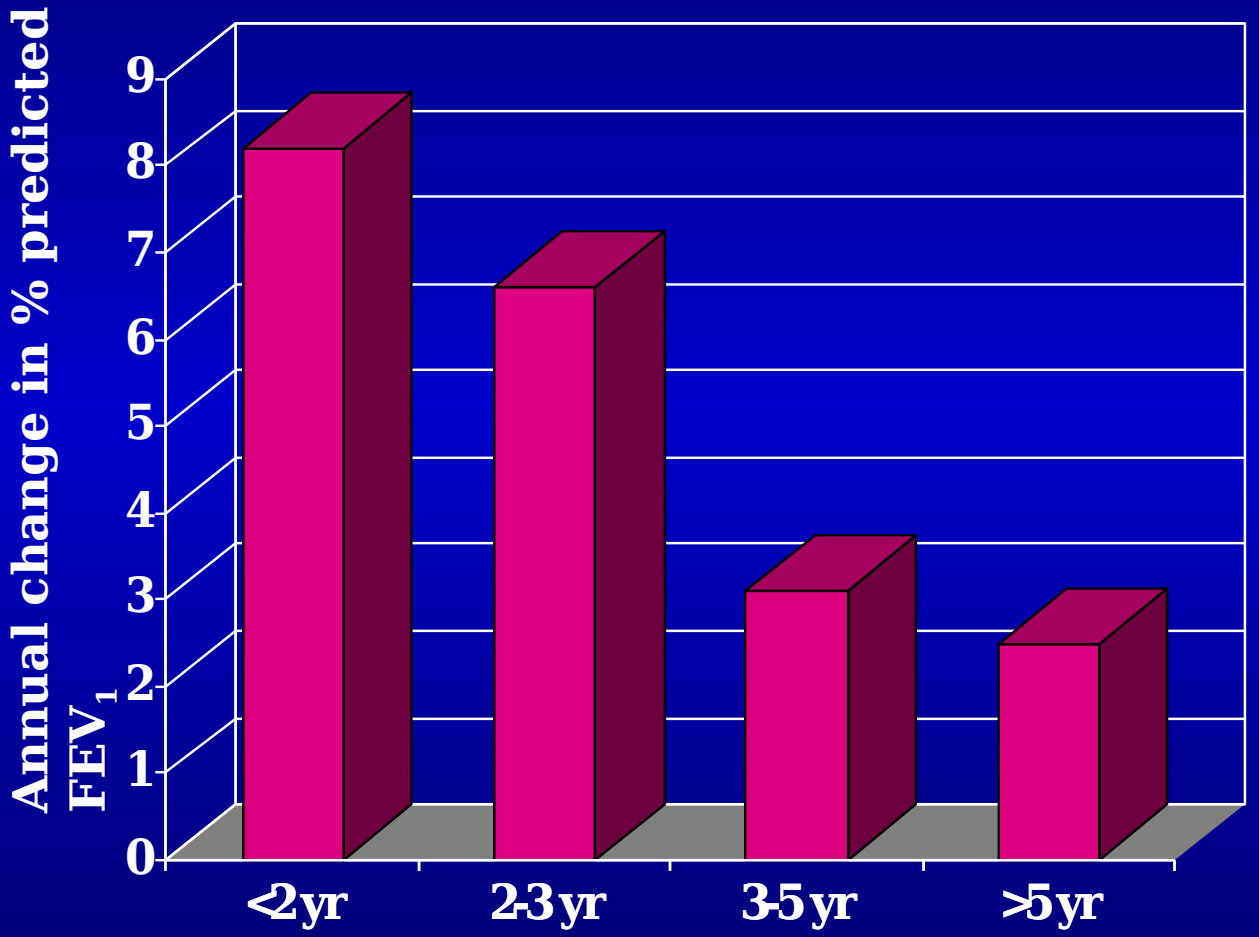
Juniper et al., Am Rev Resp Dis, 1990

Number of Hospitalizations in Patients Receiving Inhaled Steroids in Relation to Rate of ß$_2$-agonist Dispensing



Donahue et al. JAMA 1997

INFLUENCE OF ASTHMA DURATION AT THE START OF INHALED STEROIDS UPON THE MEAN ANNUAL INCREASE IN FEV_1



216 children 3-11 yrs old
62 controls 3-11 yrs old

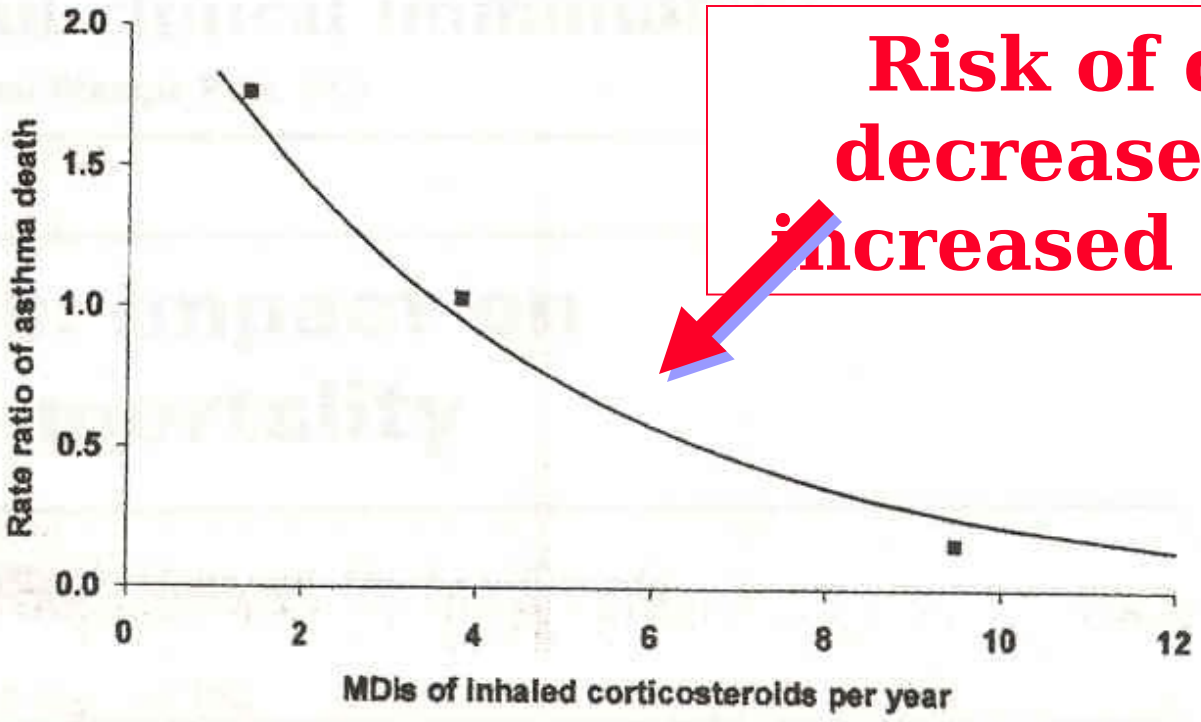
Inhaled steroid: budesonid
Dose:800mcg/day titrated

Controls: theophylline and/or cromolyn

Followed 3-6 yrs on steroid
1-2 year run-in period

No difference between gro
weight gain or growth velo

Agertoft L, Pedersen S. Respiratory Medicine 1994;88:373.



Risk of death decreases with increased ICS use

FIG 2. Fitted RR for death from asthma as a function of the number of canisters of inhaled corticosteroids dispensed in the prior 12 months. Adapted from Suissa S et al. New Engl J Med 2000;343:332-6.

Death from asthma

NEJM 2000;343:332-6

Deaths from Asthma and ICS Use

Annual asthma deaths/100,000 people

ICS sales

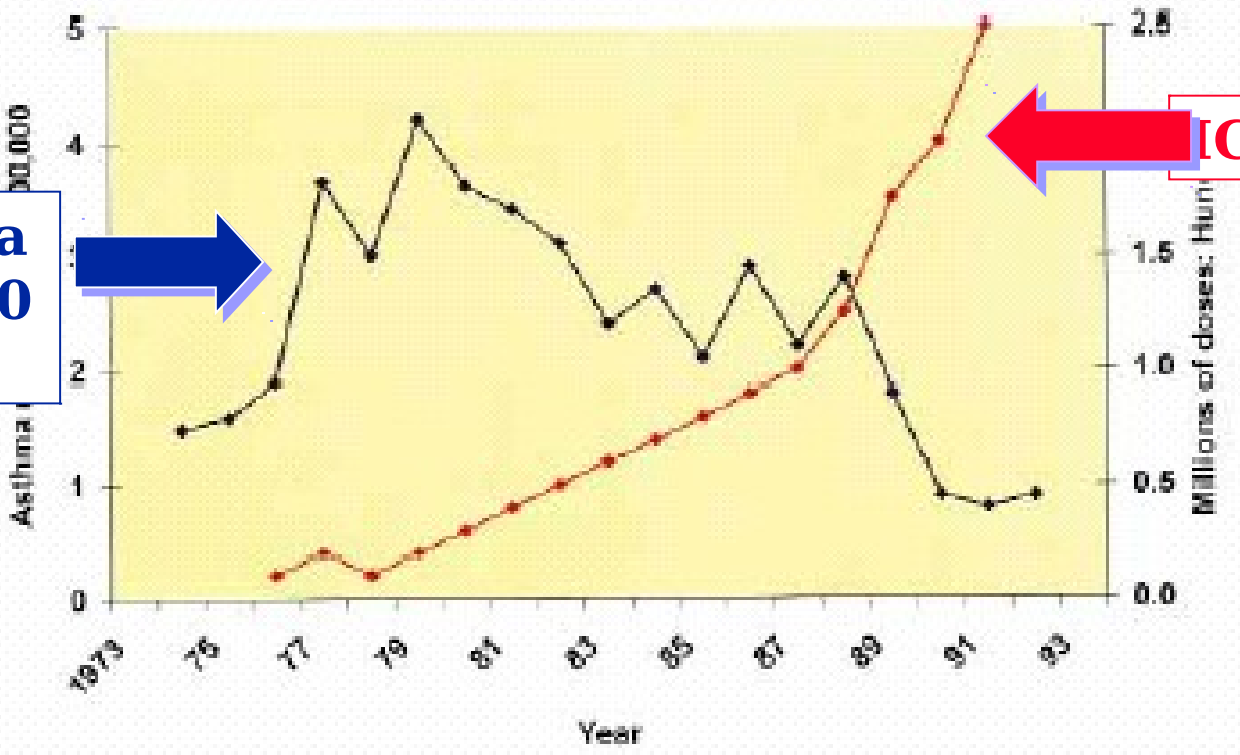


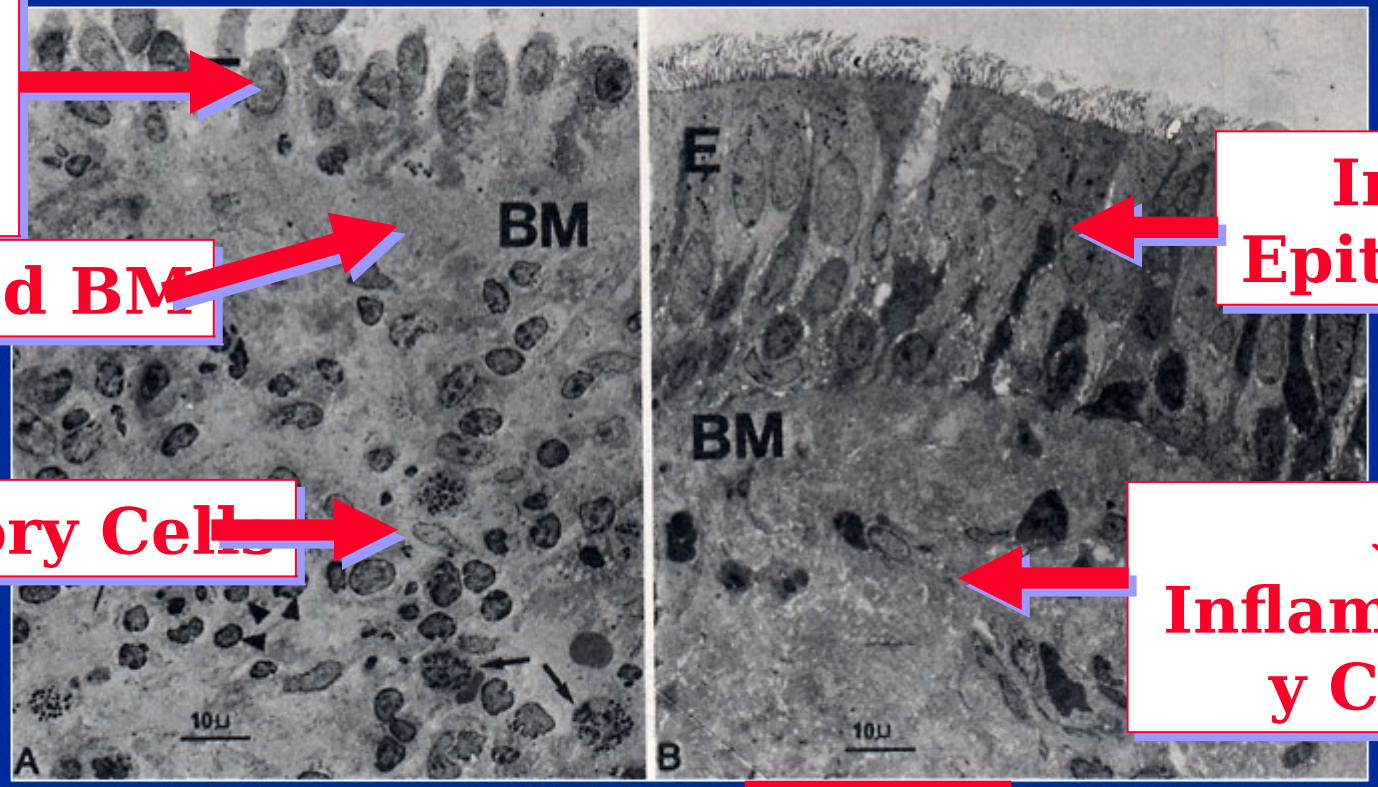
FIG 1. Yearly asthma death rates per 100,000 people 5-34 years of age *(in blue)* and inhaled corticosteroid sales in hundreds of millions of doses *(in red)* in New Zealand over the period 1976 to 1991. Adapted from Suissa S, Ernst P. J Clin Epidemiol 1997;50:1079-88.

Mechanism of Action

- Inhibit production of inflammatory cytokines
- Decrease number of eosinophils & mast cells
- Decrease mucous secretion
- ptors

Important with concomitant beta-agonist use

Effects of Inhaled Corticosteroids on Inflammation



Compromised Epithelium

Thickened BM

Inflammatory Cells

Intact Epithelium

↓ Inflammatory Cells

Pre– and post–3-month treatment with budesonide (BUD) 600 mcg BID

Laitinen et al. J Allergy Clin Immunol 1992;90:32-42

Adverse Effects

- Oral candidiasis (thrush)
- Dysphonia
- Systemic effects at high doses
  - Potential for pituitary-adrenal axis suppression
  - Osteoporosis/osteopenia
  - Growth rate suppression in children

Oral Candidiasis

- Related to total dose
- Incidence 5 - 10%
- Spacer reduces incidence
- Mouth washing helpful
  - Good recommendation: Use ICS before brushing teeth
    - Twice a day
    - Mouth gets rinsed after use

Dysphonia

- Occurs in 30-50%
- Related to total dose
- Laryngeal myopathy
  - May diagnose by rhinoscopy
- Spacers do not reduce incidence
- Maybe less common with dry powder inhalers

Pituitary-Adrenal Axis Suppression

- Marked variability from patient to patient
- Cumulative dose (inhaled, nasal, oral) important
  - Probably not clinically significant from ICS
- No current recommendation for monitoring
  - Some check annual morning serum cortisol for patients on higher total doses (>1500mcg/day)
- Rare case reports of adrenal crisis in children
- No case reports in adults

Pituitary-Adrenal Axis Suppression

- Doses of 1500-2000 mcg more frequently associated with suppression
  - Most studies looks at urinary cortisol
  - ? Clinical significance
- Daily doses of 1500 mcg in adults and 400 mcg in children show little suppression
- Budesonide 800 mcg/d and flunisolide or triamcinolone up to 1000 mcg/d caused no suppression in children
- May be caused by lower doses of fluticasone than other inhaled steroids

Osteoporosis

- Risk is not clear
  - CAMP study: children – no effect on BMD
  - NEJM 2001: adult women – decreased BMD in hip but no spine or femoral neck - ? significance
- Consider in all patients
  - Calcium daily: 1000 – 1500 mg/d
  - Vitamin D daily – 400-800 IU/d
  - Weight bearing exercise
- High dose inhaled or oral steroids
  - Bone density study
  - Specific osteoporosis therapy

GROWTH

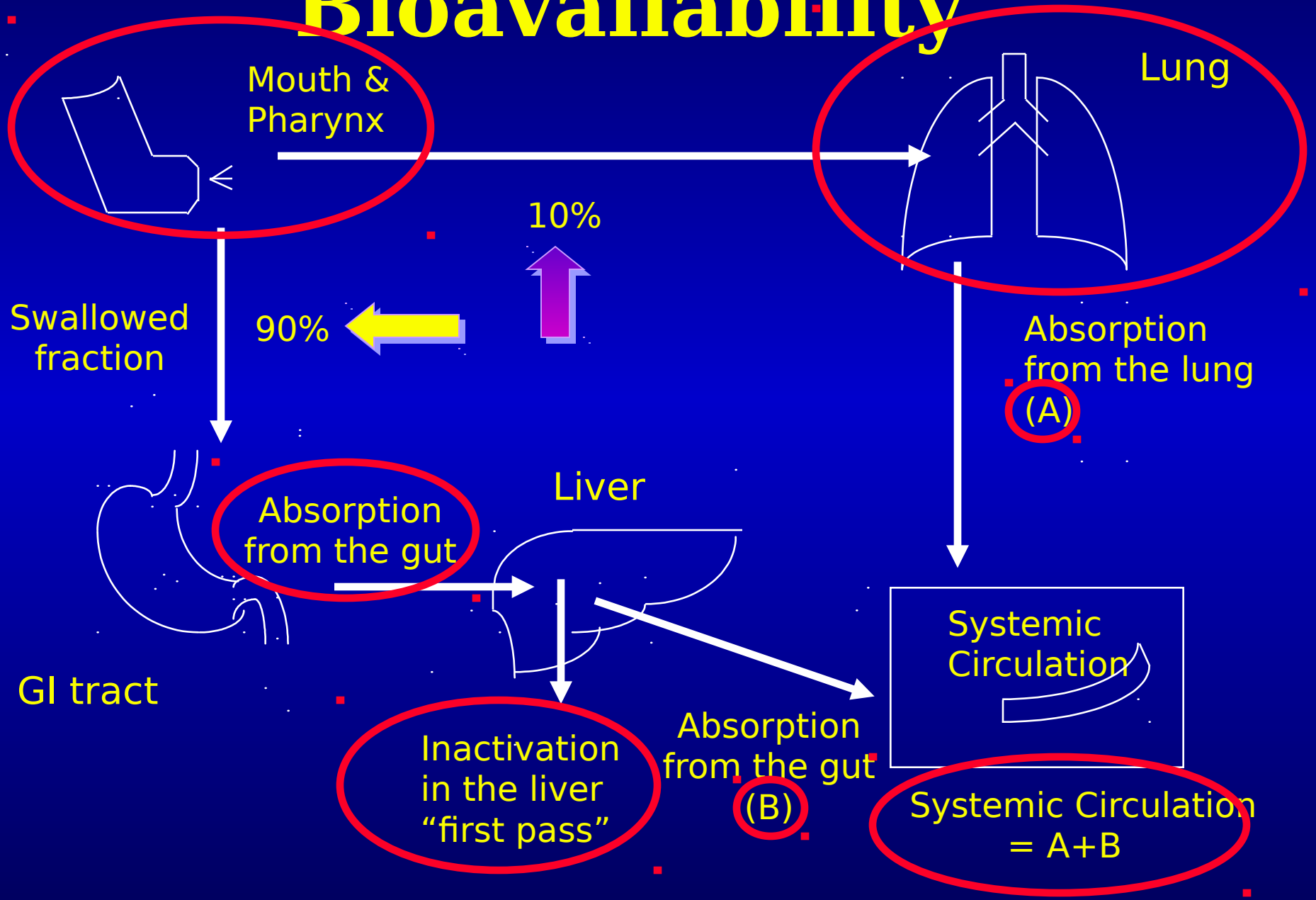
Effects on Growth

- Some studies have shown an effect on short-term growth
  - Short-term growth in children is highly variable
  - Approx. 1 cm/year less in some studies
- Some evidence that bone age is also delayed proportionately
  - Final height attained more relevant end-point
  - Long-term studies to date show no effect on adult height
- Poorly controlled asthmatics show poor growth compared to nonasthmatics

What do I tell parents?

- “At standard doses, there is no convincing evidence that inhaled steroids suppress growth”
- “At higher doses, inhaled steroids may slow growth over initial 6-12 months”
- “Final adult height does not appear to be affected”
- “Uncontrolled asthma definitely suppresses growth”
- *“Benefits far outweigh the potential risks”*

Bioavailability



Oral Bioavailability

- Majority of systemic activity comes from steroid that enters the GI tract
- 10-20% of MDI dose reaches the lungs
- 80-90% of dose is swallowed
- Spacer device increases the amount of steroid that reaches the lungs
  - Less available for systemic activity

Inhaled Corticosteroids

- Triamcinolone MDI (Azmacort)
  - 6 years and greater
- Flunisolide MDI (Aerobid)
  - 6 years and greater
- Beclomethasone MDI (Vanceril)
  - 6 years and greater (QVAR – 5yrs)
- Budesonide DPI, and RESPULES
  - Respules 12 months to 8 years, DPI-6 years
- Fluticasone MDI (Flovent)
  - Powder – 4yrs, aerosol – 12 yrs

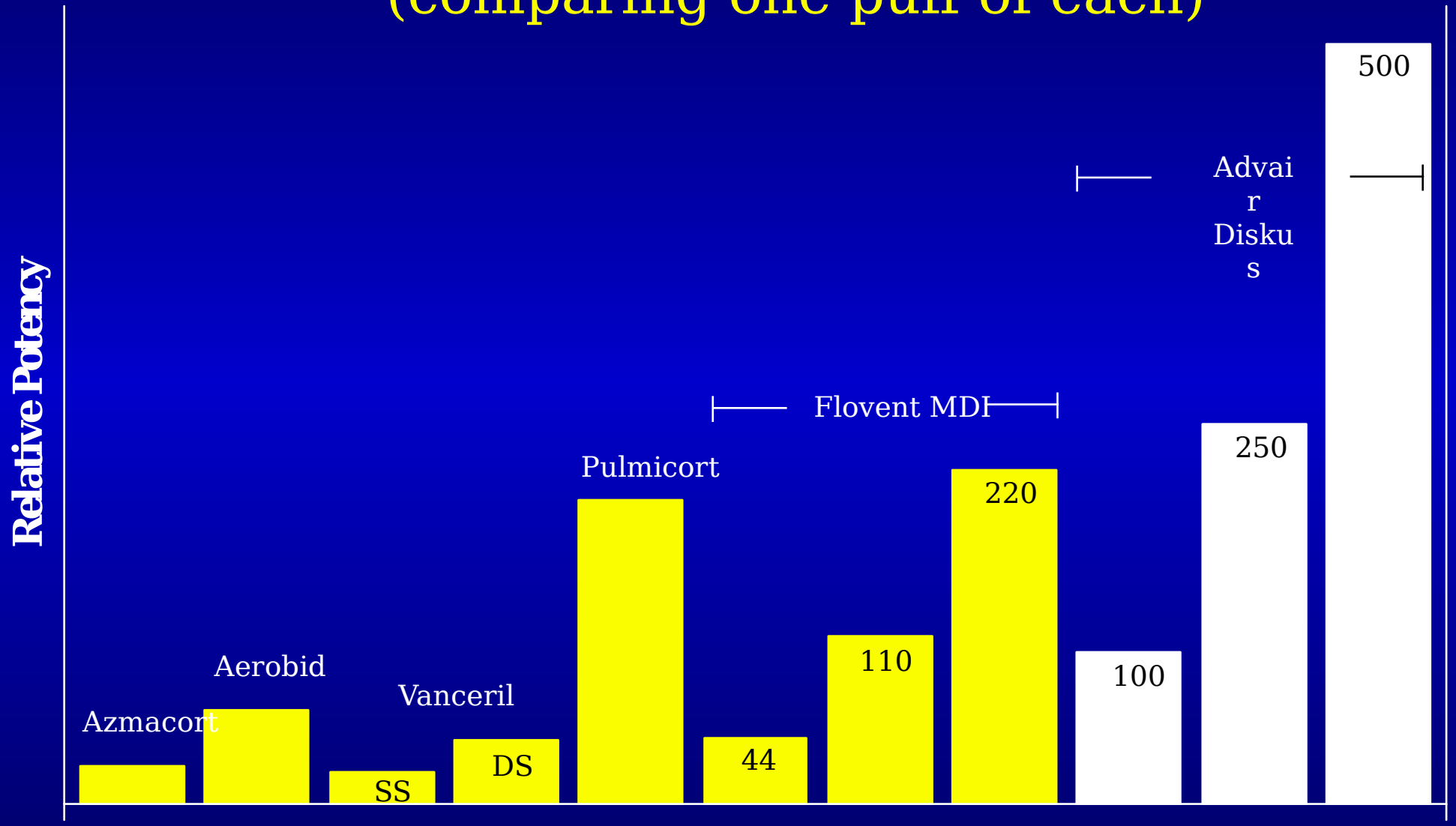
Relative Potency

- Triamcinolone MDI (Azmacort) 1
- Flunisolide MDI (Aerobid) 1?
- Beclomethasone MDI (Vanceril) 2
- Budesonide MDI 2
- Budesonide DPI (Pulmicort) 4
- Fluticasone MDI (Flovent) 4

Inhaled Steroids

Drug	mcg/puff or dose
Beclomethasone dipropionate	
Beclovent	42
Vanceril	42
Vanceril DS	84
Triamcinolone acetonide	
Azmacort	100
Flunisolide	
Aerobid	250
Fluticasone	
Flovent	44,110,220
Budesonide	
Pulmicort Turbuhaler (DPI)	200

Relative Potency of Steroid Inhalers
(comparing one puff of each)



Fluticasone propionate
(Flovent)

- Potent inhaled steroid with proven efficacy
- Potency increases risk of systemic effects
- Powder (diskus) is indicated 4 years and older and aerosol is 12 and older
- Flovent has 3 doses available and can be easily fitted for low, medium and high dose delivery

Budesonide
(Pulmicort Turbuhaler)

- Potent corticosteroid (like Flovent)
- Dry powder increases deposition in lower respiratory tract (6 years or older)
- Turbuhaler is breath-activated
  - No spacer needed
  - No CFC propellants

Pulmicort Respules (Nebulized Budesonide)

- Indication: Meets criteria for inhaled steroid for maintenance therapy but unable to reliably use MDI with spacer
  - FDA approved for children ages 12 months to 8 years of age
  - Consider in elderly patients unable to coordinate use of MDI and spacer
- Not a rescue med for an acute asthma exacerbation

Beclomethasone (BDP)/HFA (QVAR)

- Hydrofluoroalkane
  - Extra-fine aerosol that delivers smaller particles
- Improved delivery to peripheral airways
- Iincreased lung deposition compared to BDP CFC
  - QVAR 50-55% versus BDP CFC 16%
- No spacer required
  - 1/3 less pharyngeal deposition than CFC
- 2.5 fold reduction of BDP CFC dose with similar efficacy and safety profile

Triamcinolone - Azmacort

- Low dose
- Built in spacer
  - worthless
- Need to take 4 times a

Pros & Cons of Steroid Inhalers

	Pros	Cons
Azmacort	- built-in spacer	- worthless spacer
Aerobid	- low cost	- bad taste
Vanceril	- low dose	- low dose
Pulmicort	- easy to use - no spacer needed - minimal taste - effective at qd dosing	- must generate an adequate inspiration
Flovent	- high potency	- none specific

Beta Agonists

Short-acting β-2 agonists

- Mechanisms
  - β-2 agonist effects (smooth muscle relaxation due to increased cyclic AMP)
  - Repeated high dose exposure to agonist leads to down regulation of receptors
- Side effects
  - Tachycardia
  - Tremor
  - Hypokalemia, hypomagnesemia
  - Increased lactic acid
  - Hyperglycemia

ß$_2$ Agonists

Short Acting (3-6 hr)	Dose/puff
Metoproterenol (Alupent, Metaprel)	**650 mcg**
Albuterol (Proventil, Ventolin)	**90 mcg**
Bitolterol (Tornalate)	**370 mcg**
Pirbuterol (Maxair)	**200 mcg**
Terbutaline (Brethaire)	**200 mcg**

Long Acting (12 hr +)	
Salmeterol (Serevent)	**21 mcg (50 mcg in Diskus)**
Formoterol	**12 mcg**

Pharmacologic Considerations

- Oral, inhaled, subcutaneous, intravenous
- Inhaled via MDI with spacer preferred
- 10-20% of MDI dose reaches the lung
- 3-5% of nebulized dose reaches lung
- For equal bronchodilation, nebulizer requires 3-10x dose as MDI
  - Greater potential for side effects
- Nebulizer good for:
  - Young children or elderly who cannot use MDI
  - Asthma exacerbation where MDI use is difficult

Indications

- Short-acting agents are the drug of choice for acute exacerbations
- Effective for prophylaxis of exercise induced symptoms
  - Take just before exercise (15-30 min)
  - 3-6 hr window of protection
- Oral, sustained-release may be used in kids for nocturnal symptoms

Appropriate Use

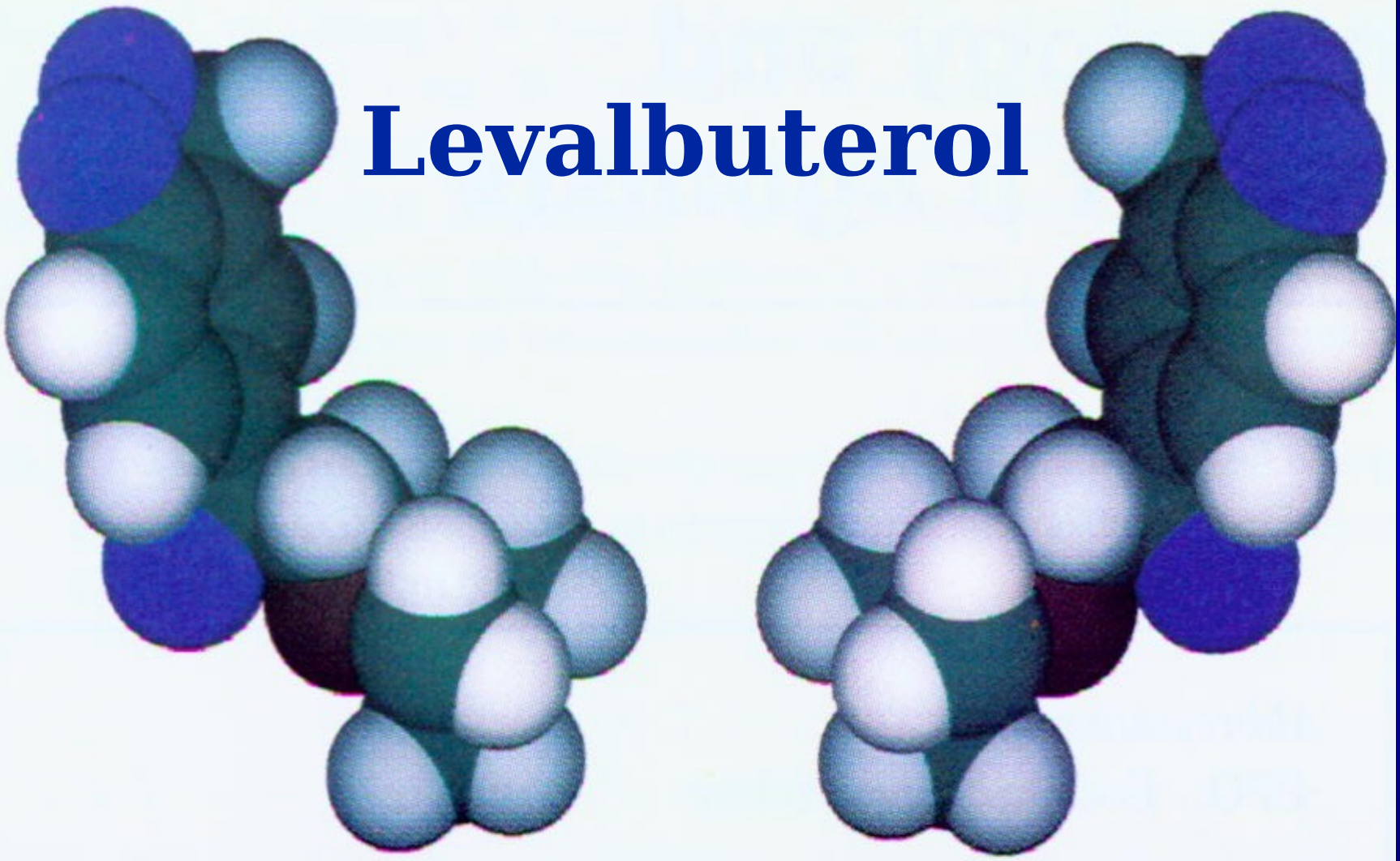
- Should be used only as needed
- Use more than twice weekly indicates need for better long-acting control
- Long-term, regularly scheduled use of short-acting ß agonists leads to diminished control

Oral β_2 Agonists

- Less effective than inhaled beta agonists
- Produce more adverse effects
- Have a slower onset of action
- May be beneficial in adults unable to use a MDI correctly and for nocturnal asthma
- Oral syrup may be useful for young children and elderly with infrequent mild symptoms who cannot use an inhaler and spacer device

***Medical Letter Vol 42 Page 20**

Levalbuterol



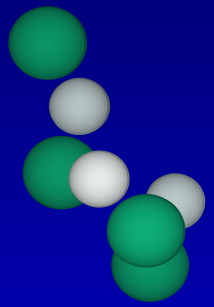
Levalbuterol

- Xopenex
- Prevention and treatment of bronchospasm
- Approved for use in age 6 years and up
- 3 ml ampules for nebulization
  - 0.63 mg, 1.25 mg doses
  - TID

Good Guy

(R)-albuterol

- Potent binding to the β_2-receptor
- ↓ Intracellular Ca^{++}; ↓ Airway reactivity
- ↓ Eosinophil activation
- Rapid metabolism
- No effect on mucus production
- ↑ Ciliary beat frequency & mucocilary transport velocity



- Very limited binding to b_2- receptor
- ↑ Intracellular Ca^{++}; ↑ Hyperresponsiveness
- ↑ Eosinophil activation; ↑ Mast cell histamine release
- Metabolized at 1/10th the rate of (R)-albuterol
- ↑ Mucus production by epithelial cells
- ↓ Ciliary beat frequency & mucociliary transport velocity

Bad Guy

(S)-albuterol

Levalbuterol

- Proposed advantages
  - Consists entirely of therapeutic (R)-albuterol
  - Contains no potentially detrimental (S)-albuterol
  - Achieves efficacy comparable to racemic albuterol with fewer β_2-mediated side effects at 0.63 mg in clinical trials
  - Produces improved bronchodilation with comparable β_2-mediated side effects at 1.25 mg in clinical trials

Levalbuterol

"Levoalbuterol…appears to have *NO* clinically significant advantage over racemic albuterol" The Medical Letter. Volume 41, Page 51.

"Levalbuterol, the R-isomer of racemic albuterol, offers no clinically significant advantage over racemic albuterol" The Medical Letter. Volume 42, Page 19.

Considerations

- Increased cost ($60/24 vials)
- Questionable effectiveness for cost ratio
  - More potent than racemic albuterol but end result is similar
  - Side effects still dose dependent in levalbuterol
- Unclear, which population, if any, will benefit the most
- Need more comparison trials with racemic albuterol

Long Acting Beta Agonists

Long-Acting Bronchodilators

	Albuterol (Proventil, Ventolin)	Salmeterol (Serevent)	Formoterol (Foradil)
Dose	2-4 puffs prn	2p q12 (MDI) 1p q12 (Diskus)	1p q12
Character	Hydrophilic	Lipophilic	Hydrophilic & Lipophilic
Onset of action	Rapid (2-5 minutes)	Delayed (>30 minutes)	Rapid (2-5 minutes)
Duration	Short (4-6 hours)	Long (12 hours)	Long (12 hours)

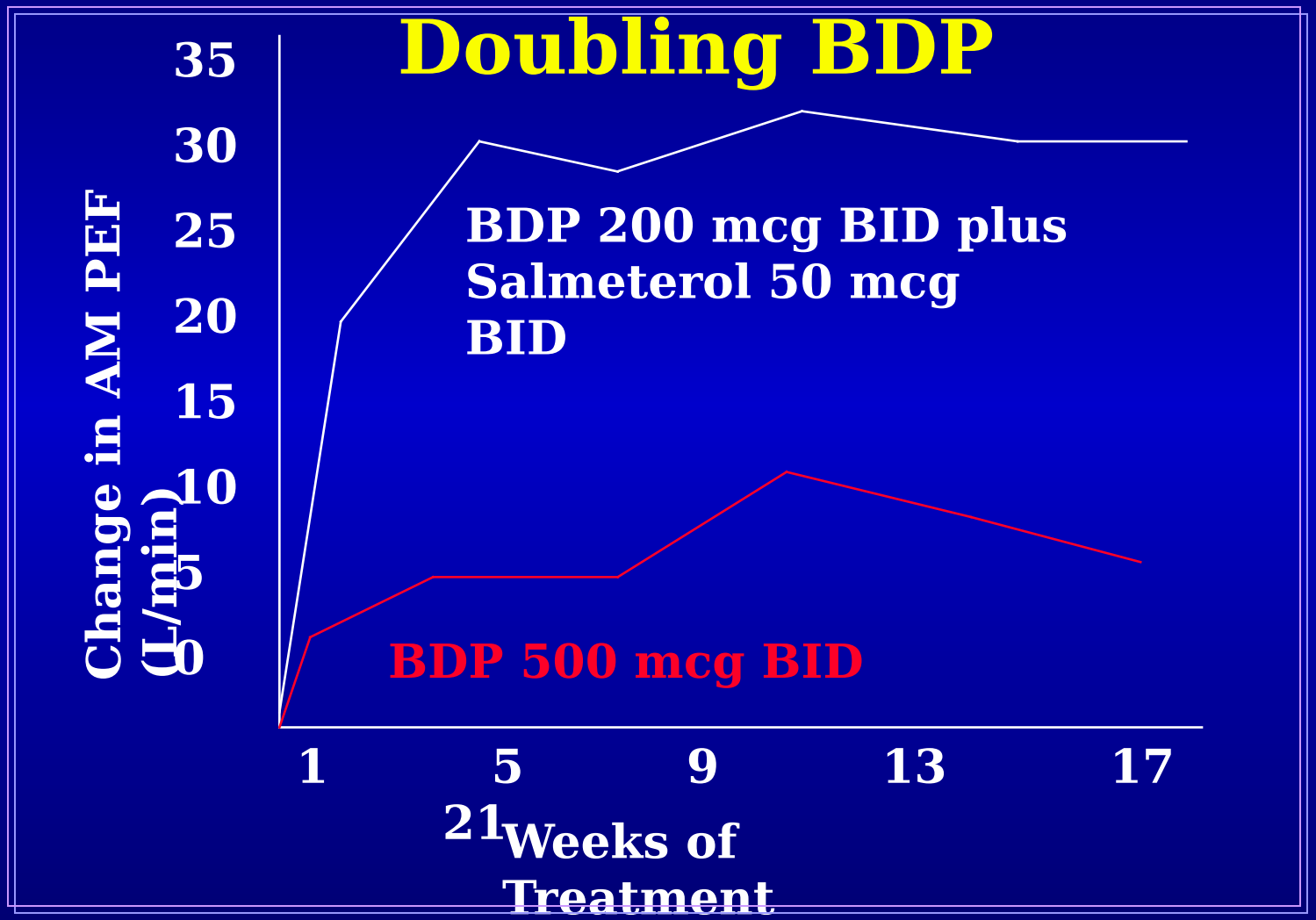
Salmeterol
(Serevent)

- Long acting beta-agonist/bronchodilator
- Binds to an exosite adjacent to the regular beta receptor
- Slower onset of action
  - maximum effect in 3 hours
- Longer duration of action (12 hours)

Salmeterol
(Serevent)

- Exhibits bronchoprotective effects
  - Allergen challenge
  - Exercise challenge
  - Histamine/methacholine challenge
- Anti-inflammatory effects in animal studies
  - No evidence that these are clinically significant in asthma patients

Addition of Serevent Improves Asthma Control More than Doubling BDP



Ann Allergy Asthma Immunol 82:257, 1999 and 82:383, 1999. Thorax 54:207, 1999

Salmeterol
(Serevent)

- Approved for use in children with asthma
  - DPI: 4 years and older
  - Aerosol: 12 years and older
- Dose 25-50mcg (1-2 puffs) twice daily
- Side effects similar to other beta-agonists
  - Headache
  - Tremor
  - Tachycardia
  - Palpitations

Salmeterol MDI
(Serevent)

- Slow onset bronchodilator
  - NEVER a rescue medication
- Long duration of action
  - Ideal for patients with nocturnal symptoms
- Effective bronchoprotection
  - Ideal for prophylaxis of exercise asthma
- Lack of anti-inflammatory action

Does Asthma Drug Trigger Attacks? December 17, 2003

CBSNEWS.com HOME

Jim and Star Chavez didn't think twice when their doctor prescribed Advair for their son Ethan.
Inhaled daily, Advair was supposed to prevent his occasional mild asthma attacks. Instead, as CBS News Correspondent Sharyl Attkisson reports, **shortly after he started using Advair, Ethan collapsed**.
"He was totally lifeless," says Jim Chavez. "His eyes were rolled back in his head, and it was really terrifying."
"I shook him, and I kept on shaking him and kept on yelling his name, 'Ethan, Ethan, wake up, wake up,' and he wouldn't respond at all," says Star Chavez.

They didn't know it then, but asthma patients taking the same medicine in a study were dying in unexpected numbers.

Drugmaker GlaxoSmithKline led a study of Salmeterol, the medicine in Advair and another Glaxo asthma product, Serevent. Designed to relieve asthma, it seemed to trigger fatal attacks in some. Three times more patients taking the medicine died of asthma than those not taking it.
A safety monitoring board took one look at the deaths and shut down Glaxo's study. The FDA recently forced Glaxo to disclose the small but significant risk of death in a black box warning on its medicine and in ads: "Rare but serious asthma episodes and asthma related fatalities occurred."
In the study, Glaxo found deaths among blacks were the highest, though white deaths were also elevated. Glaxo then sent out a carefully worded message that led some to believe white patients need not worry: "These risks may be greater in African-Americans."

Yet CBS News has learned a study ten years ago of only white patients also found an increase in asthma deaths. Glaxo dismissed the deaths back then as "probably due to the disease rather than the treatment."
Most people who use Advair have no serious problems, and the FDA says benefits outweigh risks. And despite the new warnings, sales have increased, approaching $2 billion a year.

And that black box warning ordered for Advair four months ago still isn't on the product. The FDA says Glaxo negotiated when it will be but won't tell CBS News the date.

Ethan has fully recovered from his trauma, and the whole family is breathing easier without the asthma remedy that may have been worse than the disease.

SMART Trial

- Salmeterol Multi-center Asthma Research Trial
- Compare serevent and placebo in the treatment of asthma
- Interim analysis in 2002:
  - Treatment group: 13,174, Placebo group: 13,179
- No difference in respiratory related deaths – primary endpoint
- Secondary endpoints
  - Greater number of asthma-related deaths in the serevent group (13 vs. 4)
  - Greater number of asthma-related deaths or life-threatening experiences in the serevent group (36 vs. 23)
  - Not statistically significant

SMART Trial

- Subpopulation analysis
  - No differences among Caucasian subjects (71%)
  - African Americans (17%) had a statistically significant greater number of:
    - Primary events in salmeterol group (20 vs. 7)
    - Asthma-related death (8 vs. 1)
    - Asthma-related death or life-threatening experience (19 vs. 4)
  - Less than 1% of all African Americans in the study experienced an event
- Significantly higher number of deaths in patient taking salmeterol without an ICS

SMART Trial

- **Final points**
  - **Small increase in respiratory mortality in African Americans**
  - **Numbers were extremely small**
  - **Many were not using concomitant ICS**
- **Benefits of salmeterol far outweigh the small risks**
- **Only use salmeterol with an ICS**

Combination Drugs

ADVAIR DISKUS
100/50
ADVAIR DISKUS
250/50
ADVAIR DISKUS
500/50

Fluticasone/Salmeterol DPI (Advair)

- Proven as effective as combination therapy with separate flovent and serevent inhalers
- Improves compliance
  - Only one inhalation twice a day required
- Diskus dry powder inhaler
  - Must instruct on delivery technique
  - Shows number of remaining doses

Combivent

- Ipratropium/Albuterol
- Indicated for COPD for patients who were not controlled with single therapy
- Not FDA approved for use in asthma
- Contraindicated with soy allergy
  - Some dosage forms may contain soya lecithin

Ipratropium bromide
(Atrovent)

- Important in COPD
- No benefit in chronic treatment of asthma
- May have some benefit along with inhaled beta-agonists in acute asthma exacerbations
- Can give in nebulizer mixed with albuterol

Leukotriene Modifie

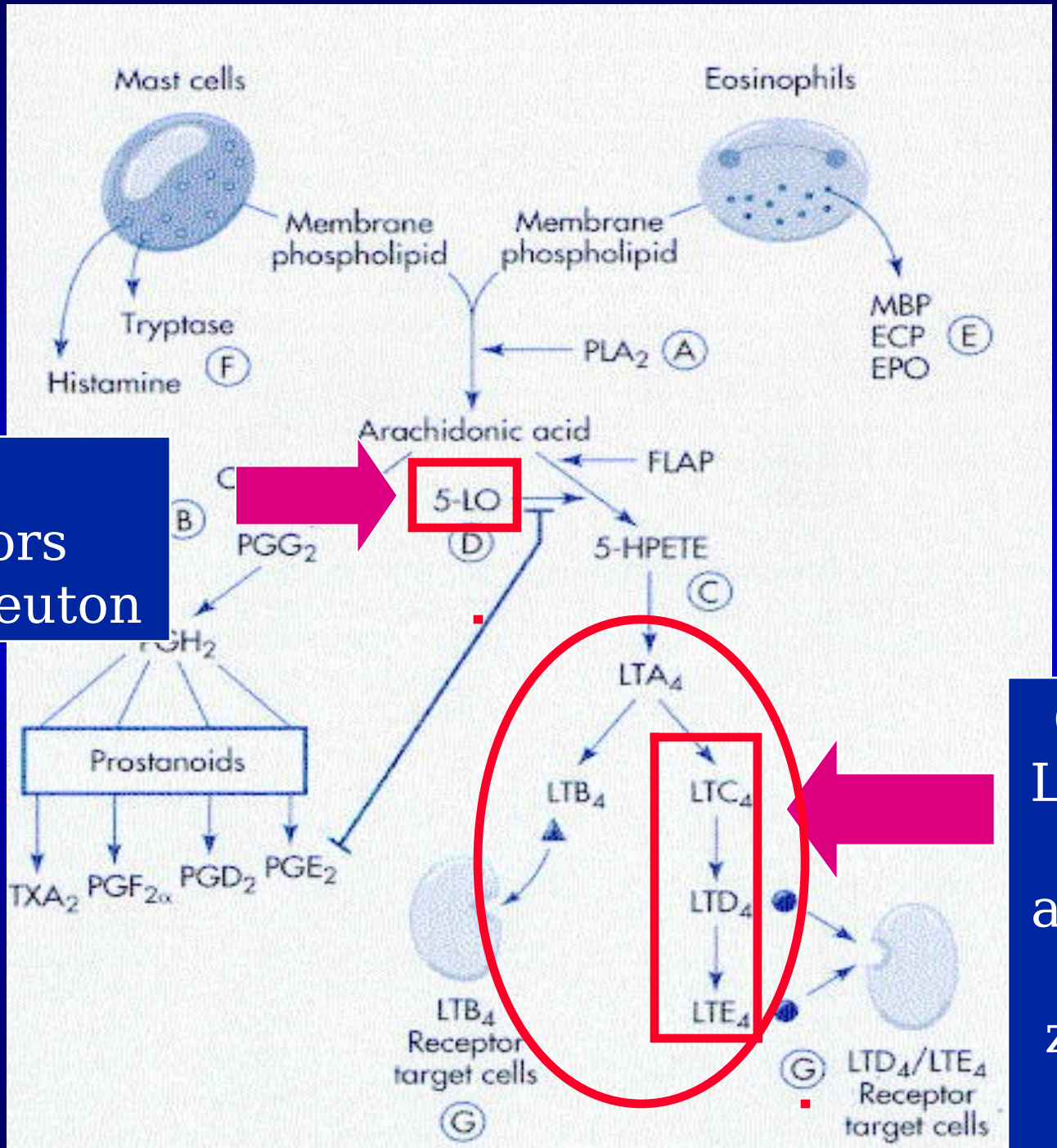
Leukotriene Modifiers

- Leukotrienes are one of many mediators active in patients with asthma
- Cysteinyl LT's have major role in asthma
  - Bronchoconstriction
  - Airway hyperresponsiveness
  - Vascular permeability
  - Increased mucous production
- LTB_4 less well understood
  - Neutrophil chemoattractant
  - Possibly an eosinophil chemoattractant

Leukotriene Modifiers

- Zileuton (Zyflo)
  - Inhibits 5-lipoxygenase
  - Blocks production of all leukotrienes
- Zafirlukast (Accolate)
  - Leukotriene receptor antagonist
  - Blocks only effects of LTC_4, D_4, E_4
- Montelukast (Singulair)
  - Newest agent
  - Also leukotriene receptor antagonist

5-LO inhibitors
- zileuton



Cysteinyl-LT receptor

antagonists
-
zafirlukast
-
montelukas

Clinical Effects

- Increase in FEV_1 by 10-15%
- Reduces
  - Beta-agonist use
  - Daytime and nocturnal symptoms
- Often used in combination with inhaled steroids
  - Potentially first-line in mild asthma
  - Consider in mild asthma and allergic rhinitis
- Treatment of choice in aspirin-sensitive asthma

Montelukast (Singulair)

- Dosing:
  - ages 15 & older: 10 mg po daily
  - ages 6-14: 5 mg chewable dose daily
  - ages 2-5: 4 mg chewable dose daily
- Recommended to take dose in the evening
- Can be taken with or without food
- No known drug interactions
- No significant side effects to date

Zileuton (Zyflo)

- 600 mg po four times a day
- Drug interactions
  - Theophylline, propranolol, warfarin
- Monitor hepatic function
  - Every month x 3 months
  - Then every 3-4 months
- Can take without regard to meals
- Approved for use down to age 12

Zafirlukast (Accolate)

- 20 mg po BID
- Drug interactions
  - Warfarin, aspirin, theophylline, erythromycin
- Rare hepatic events reported
- Rare cases of Churg-Strauss
- Absorbed poorly with food
  - Take 1 hour pre- or 2 hours post-meals
- Approved for use down to age 12

Other Asthma Medications

Cromolyn sodium and Nedocromil

- Block chloride channel of mast cells
  - Mast cell stabilizers
  - Decrease histamine release
- Inhibit neutrophil chemotaxis
- Nedocromil also inhibits eosinophil degranulation

Clinical Effects

- Inhibits both the early and late phase response to allergen challenge
- Protects against bronchospasm
  - Exercise
  - Cold air
  - Many other triggers
- Reduces bronchial hyperreactivity

Cromolyn Sodium

- Relatively weak compared to steroids
- No significant side effects
- Ages for administration
  - MDI (1 mg/puff)- 5 years and older
  - Nebulizer solution- 2 years and older
  - Capsule - 5 years and older
- Dose
  - MDI (1mg/puff): 2-4 puffs TID-QID
  - Nebulizer: 1 ampule TID-QID
  - 1 Capsule: QID---BID

Nedocromil Sodium

- Available as MDI only
  - 1.75 mg/puff
- Indicated for mild to moderate asthma
- Dose 2-4 puffs QID --- BID (taper)
- 190 times more potent than Cromolyn
- 20% complain of bad taste

Theophylline

Methylxanthenes - Theophylline

- Smooth muscle relaxation from phosphodiesterase and possibly adenosine antagonism
- Downregulates function of inflammatory cells
- Inhibits eosinophil migration into mucosa
- Decreases diaphragmatic fatigue
  - Increases diaphragm contractility
- Increases mucociliary clearance

Clinical Effects

- Theophylline is clinically more effective for long term control than:
  - Cromolyn
  - Oral and inhaled short-acting beta agonists
- Benefit shown when added to inhaled steroids
- Less effective than
  - Salmeterol
  - Inhaled steroids
- Equal to zileuton (other anti-leukotrienes not tested)
- Drawbacks
  - Adverse effects, risk of toxicity, routine blood levels

Toxicity

- Nausea, vomiting, diarrhea
- Irritability, insomnia
- Seizures, hyperthermia, brain damage
- Hyperglycemia, hypokalemia, hypotension, arrhythmias
- **Must monitor levels**

Drug Interactions

Increase Levels

- alcohol
- cimetidine
- ciprofloxacin
- clarithromycin
- erythromycin
- OCP/estrogens
- verapamil
- zileuton

Decrease Levels

- aminoglutethamide
- carbamazepine
- isoproterenol
- phenobarbital
- phenytoin
- rifampin
- sulfinpyrazone

Other Factors

Increase Levels	Decrease Levels
- fatty foods	- food
- carbohydrates	- high protein diet
- febrile illness	- age 1-16
- CHF	- smoking
- neonates, elderly >60	

Omalizumab (Xolair)

- Recombinant, humanized, mouse anti-IgE antibody
- SQ injection every 2-4 weeks
- Dose based on serum IgE level and weight
- Indications:
  - Moderate-severe asthmatics
  - Atopic (positive aeroallergen skin test or RAST)
  - Incomplete symptom control on ICS
  - >12 years old

Omalizumab (Xolair)

- Benefits compared with placebo:
  - Larger median ICS dose reduction (83 versus 50 percent)
  - Higher percentage of patients able to discontinue ICS (43 versus 19 percent)
  - Fewer exacerbations
- Risks:
  - Anaphylaxis (0.1%)
  - Non-significant trend toward increase malignancy
- Cost: $10,000-$12,000/year

Alternative Therapies

- Cyclosporine
- Methotrexate
- Gold
- Colchicine
- Hydroxychloroquine
- Nebulized Lidocaine
- Nebulized Heparin
- IVIG
- Dapsone
- Macrolide Antibiotics

Asthma Treatment Summary

Mild Intermittent

Use: Albuterol, Asthma Action Plan

Mild Persistent

Use: Albuterol and Controller medications (low dose steroids, nedocromil, cromolyn, montelukast)

Moderate Persistent

Use: Combination of medications (low to medium dose steroid plus long acting beta agonist, and/or Leukotriene modifiers)

Severe Persistent

Use: High dose inhaled steroids, long acting beta agonist, and leukotriene modifier. May need oral steroids

Step Down Therapy

- **Don’t Forget This Part!**
- Gradually reduce long term control medications after several weeks/months of controlling persistent asthma
  - Review treatment every 1-6 months
  - Reduce ICS about 25% every 2-3 months until the lowest dose required to maintain control is obtained

The End

Any Questions?